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(Accepted 9 March 1987)

Effects of intradermal bradykinin after inhibition of angiotensin converting enzyme

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Abstract

Inhibitors of angiotensin converting enzyme may cause angio-oedema. To see if this might be due to potentiation of the tissue effects of bradykinin the thickness of weals raised by intradermal injection of saline or 1, 3, or 10 µg bradykinin was measured before and three times after single doses of captopril, enalapril, or placebo. The mean thickness increased with increasing doses of bradykinin. It did not change with time after the administration of placebo or captopril but increased from 0.61 mm before enalapril to 1.12 mm two and a half hours and 1.06 mm five hours after enalapril was given. Five subjects flushed when given bradykinin after captopril and four after enalapril, but none flushed when given bradykinin after placebo.

It is concluded that angiotensin converting enzyme inhibitors potentiate the effects of intradermal bradykinin in vivo and that this may partially explain why they cause angio-oedema in susceptible patients.

Introduction

Angio-oedema is an occasional but potentially fatal adverse reaction to angiotensin converting enzyme inhibitors. It occurs with both captopril and enalapril,^{1,2} and often develops within 48 hours after treatment is started.³ Bradykinin, a nonapeptide that causes vasodilatation and increased vascular permeability, has been implicated in the pathogenesis of the angio-oedema⁴ as it is inactivated by two distinct proteases, one of which (kininase II) is identical with angiotensin converting enzyme.⁵ Treatment with captopril increases the effect of intra-arterial bradykinin on forearm blood flow.⁶ Blood concentrations of bradykinin do not seem to be increased during treatment with angiotensin converting enzyme inhibitors.⁷ Thus the development of angio-oedema in patients receiving angiotensin converting enzyme inhibitors may be due to the reduced destruction of bradykinin formed locally in subcutaneous tissues. To investigate this possibility we studied the effects of angiotensin converting enzyme inhibitors on dermal weals induced by bradykinin.

Subjects and methods

We studied six healthy subjects aged 22-45 with normal full blood count, urea and electrolyte concentrations, and results of biochemical tests of liver function. None had any history of cardiovascular disease, hypertension, or drug allergy or was taking any medicine. All gave written informed consent to the study, which was approved by the university ethics committee. The subjects fasted from midnight before each study, and each received on separate occasions oral captopril 25 mg, enalapril 10 mg, or lactose placebo in identical capsules according to a randomised double blind trial design.

Solutions of bradykinin (Sigma Chemical Co Ltd, Poole, Dorset) in 0.9%

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saline were prepared on each experimental day to give concentrations of 10, 30, and 100 mg/l. Solutions were sterilised with a 0.22 µm filter (Millipore Corporation, Bedford, Massachusetts) and stored on ice until used. Two groups of four injection sites were marked on the volar aspect of each arm and 100 µl injections of saline containing 0, 1, 3, or 10 µg bradykinin administered intradermally at one group of marked sites chosen at random. Skin thickness was measured in duplicate with modified Harpenden callipers⁸ before and 20 minutes after the injection of bradykinin as preliminary experiments showed that the thickness of the weal was maximum at this time. Averages of all duplicate measurements were calculated. The response to each dose of bradykinin was calculated as the average increase in thickness of the bradykinin weal minus the average increase in thickness of the weal after administration of saline at the same time. Supine and standing blood pressures and pulse rate were measured by sphygmomanometry (Hawksley random zero sphygmomanometer) and palpation of the radial artery, respectively. Dose-response curves to intradermal bradykinin, blood pressure, and pulse rate were assessed just before and at two and a half, five, and seven and a half hours after administration of the drugs.

The mean responses to each dose of bradykinin and at each time were compared by within subject analyses of variance separately for each of the three treatments. Reanalysis using square root transformation produced homoscedasticity but made no difference to the conclusions so untransformed data are presented here. Two tailed tests were used, and differences were taken to be significant at $p < 0.05$. The GLIM computer system was used for the analyses of variance and to obtain the standard error of the differences between pairs of means⁹; this enabled pairs of means to be compared by t tests when significant effects were found in the analyses of variance. In this analysis the degrees of freedom for the t statistic are those of the appropriate error term in the analysis of variance—namely, (No of subjects - 1) × (No of doses - 1) or (No of subjects - 1) × (No of time points - 1).

Results

Table I shows the mean increases in weal thickness for each treatment, averaged over all subjects and all times, for the three different doses of bradykinin. The standard errors of the differences between pairs of means are also given. For each treatment 10 µg bradykinin produced a significantly greater response than 3 µg ($t_{10} = 7.1, 9.5$, and 9.2 for captopril, enalapril, and placebo, respectively; $p < 0.001$ for all), but the effect of 3 µg was not significantly different from that of 1 µg.

Table II shows the mean increases in weal thickness for each treatment, averaged over all subjects and doses, at each of the four times at which

TABLE I—Mean increase in skin weal thickness (mm) 20 minutes after intradermal injection of bradykinin by dose

Treatment	Bradykinin dose (µg)			SE*
	1	3	10	
Placebo	0.34	0.47	1.13†	0.07
Captopril 25 mg	0.37	0.48	1.02†	0.08
Enalapril 10 mg	0.48	0.64	1.48†	0.09

*SE of difference between pairs of means.

† $p < 0.001$ Compared with 3 µg dose.

TABLE II—Mean increase in skin weal thickness (mm) 20 minutes after intradermal injection of bradykinin related to time after treatment

Treatment	Time after treatment (h)				SE*
	Before treatment	2.5	5	7.5	
Placebo	0.66	0.67	0.67	0.58	0.08
Captopril 25 mg	0.57	0.71	0.60	0.61	0.09
Enalapril 10 mg	0.61	1.12†	1.06†	0.68	0.10

*SE of difference between pairs of means.

† $p < 0.001$ Compared with pretreatment mean.

bradykinin was given. The standard errors are also shown. The mean responses to bradykinin were similar before and at all times after the administration of placebo. The administration of captopril caused no significant change in the response to bradykinin. A significant increase in the mean response was, however, observed two and a half hours ($t_{15} = 4.9$, $p < 0.001$) and five hours ($t_{15} = 4.4$, $p < 0.001$) after the administration of enalapril. There was no significant change in blood pressure or heart rate with either drug.

All subjects experienced mild pain 20-30 seconds after the injection of 10 µg bradykinin and sometimes after the injection of the 3 µg dose, but neither angiotensin converting enzyme inhibitor seemed to increase the intensity or duration of the pain.

During the study most subjects noticed a sensation of facial burning and appeared flushed three or four minutes after the administration of bradykinin. In some instances the flushing was accompanied by conjunctival suffusion, nasal stuffiness, and cough. When the trial had been completed it was evident that the symptoms had occurred only after the subjects received angiotensin converting enzyme inhibitors. No subject experienced the symptoms after placebo or before the administration of either inhibitor. Five subjects flushed when bradykinin was given two and a half hours after captopril but not subsequently; and four subjects flushed each time that bradykinin was given after enalapril.

Discussion

This study showed that angiotensin converting enzyme inhibitors may potentiate the effects of intradermal bradykinin in healthy subjects. Enalapril produced an unequivocal increase in the weal response to intradermal bradykinin, and after receiving the enzyme inhibitors subjects developed symptoms and signs (facial flushing, conjunctival suffusion, nasal stuffiness, cough) attributable to the effects of systemic bradykinin. These effects presumably occurred as a result of diminished metabolism of bradykinin in the skin and its consequent absorption into the systemic circulation. The absence of any enhanced local effect of bradykinin after administration of captopril may be due to captopril's comparatively short half life and the low dose used in this study. The time course of the response to bradykinin after enalapril is compatible with enalapril's duration of action.¹⁰

The finding that angiotensin converting enzyme inhibitors potentiate the effects of intradermal bradykinin partly explains the development of angio-oedema with these drugs. It may also partially explain the flushing and cough that have been associated with these compounds in some patients.¹¹ Detailed studies of such patients are needed to show whether they have abnormalities of bradykinin production, sensitivity, or destruction that are exacerbated by the inhibition of angiotensin converting enzyme (that is, kininase II).

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(Accepted 5 March 1987)